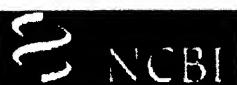


Exhibit 6

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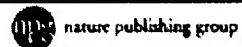
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1: Bone Marrow Transplant. 2007 Mar 12; [Epub ahead of print]



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Rapamycin, not cyclosporine, permits thymic generation and peripheral preservation of CD4(+)CD25(+)FoxP3(+) T cells.

Coenen JJ, Koenen HJ, van Rijssen E, Kasran A, Boon L, Hilbrands LB, Joosten I.

[1] Department of Bloodtransfusion and Transplantation Immunology, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands [2] Department of Nephrology, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands.

Graft-versus-host-disease (GVHD) is the most common cause of poor outcome after allogeneic stem cell transplantation (SCT). Of late, exploitation of FOXP3(+) regulatory T-cell (T (REG)) function is emerging as a promising strategy in suppression of GVHD, while preserving graft-versus-leukemia (GVL). Cyclosporine and rapamycin reduce the expansion of effector T cells by blocking interleukin (IL)-2, but signaling by IL-2 is pivotal for T(REG) homeostasis. The resolution of GVHD is critically dependent on thymus-dependent reconstitution of the immunoregulatory system. Thus, there has been concern about the impact of blocking IL-2 signaling by immunosuppressive agents on T(REG) homeostasis. Here we demonstrate in a mouse model that in contrast to rapamycin, cyclosporine compromises not only the thymic generation of CD4(+)CD25(+)FoxP3(+) T cells but also their homeostatic behavior in peripheral immune compartments. Treatment with cyclosporine resulted in a sharp reduction of peripheral CD25(+)FoxP3(+) T cells in all immune compartments studied. Prolonged rapamycin treatment allowed for thymic generation of CD4(+)FoxP3(+) T cells, whereas treatment with cyclosporine led to a reduced generation of these cells. In conclusion, cyclosporine and rapamycin differentially affect homeostasis of CD4(+)FoxP3 (+) T(REG) in vivo. As peripheral tolerance induction is a prerequisite for successful treatment outcome after allogeneic SCT, these findings are of potential clinical relevance. Bone Marrow Transplantation advance online publication, 12 March 2007; doi:10.1038/sj.bmt.1705628.

PMID: 17351648 [PubMed - as supplied by publisher]

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Lymphopenia and interleukin-2 therapy alter homeostasis of CD4+CD25+ regulatory T cells. [Nat Med. 2005]

Oral tolerance induction with antigen conjugated to cholera toxin B subunit generates both Foxp3+CD25+ and Foxp3-CD25- CD4+ regulatory T cells. [J Immunol. 2006]

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